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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,491	12/27/2001	Shuyuan Zhang	29853/37706	9920

7590 08/08/2006

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,491	ZHANG ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-78 and 80-226* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-78 and 80-226* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's argument and amendments of 6/12/06 have been entered.

Claims 70, 72, 73, 149, 163, 165, 166, 194, 196, and 197 have been amended.

Claim 79 has been cancelled.

Claims 70-78 and 80-226 are presently pending and considered.

Claim Status Cancelled Claim

In light of Applicant's cancellation of claim 79, all objections and/or rejections of such claims are rendered moot, and thus, are withdrawn.

Appendix Submitted with Argument of 6/12/06

It is noted that Applicant submitted an appendix of a declaration of Dr. Zhang, submitted in another Application. Although the material relied upon has been considered, the Declaration has not been considered as a declaration in this case, due to the form in which Applicant submitted such declaration. If Applicant wishes this to be Declaration in the instant Application, Applicant should resubmit the declaration, following regular declaration practice.

Claim Objections

In light of the amendments, the objections to Claims 149-150 are withdrawn.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 70-78 and 80-226 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-28, 31, and 33-37 of copending Application No. 09/203,078, for reasons of record.

Double-Patenting over 09/203,078 held in Abeyance

In accord with Applicant's request, the provisional double-patenting rejection over U.S. Application No. 09/203,078 is maintained, but remain held in abeyance (Applicant's response of 6/12/06, p. 30).

Claim Rejections - 35 USC § 112 – New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 78, 109, 140, 171, and 202 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims encompass the limitation that the adenoviral composition be "essentially free of BSA". Applicant argues that the specification provides support for such limitation on page 72, paragraph 2, where it says that the compositions should be essentially free of pyrogens as well as other impurities that could be

harmful to humans or animals (Applicant's argument of 10/28/05, p. 2, paragraph 1). However, such does not equate to the scope Applicant claims, and the Examiner has only found implicit support for such limitation, in the form of a specific method which produces BSA levels below the detection limit of a western blot assay (EXAMPLE 6), hence, outside of the specific embodiment of making the virus in EXAMPLE 6, Applicant has no support for the wide breadth claimed.

Response to Argument – New Matter

Applicant's response of 6/21/06 has been fully considered but is not found persuasive.

Applicant's response is to propose the option of re-amending those claims (p. 23).

Such is not persuasive. Applicant has not so re-amended those claims, so it is impossible to assess such option.

Claim Rejections - 35 USC § 112, first paragraph, critical element

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of Applicant's argument, the rejections of Claims 70-87, 91-118, 122-149, 153-180, 184-211, and 215-226 under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling, are withdrawn.

The rejection is withdrawn on the basis that, although Applicant has provided no direction or guidance for the use of such viruses without transgenes, the prior Art recognized the use of ONYX adenoviruses as therapeutic adenoviruses.

Claim Rejections - 35 USC § 112, second paragraph, essential element

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of Applicant's argument, the rejections of Claims 70-87, 91-118, 122-149, 153-180, 184-211, and 215-226 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements, are withdrawn.

The rejection is withdrawn because although Applicant has provided no direction or guidance for the use of such viruses without transgenes, the prior Art recognized the use of ONYX adenoviruses as therapeutic adenoviruses.

Claim Rejections - 35 USC § 112 - Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of the Arguments provided, the rejections of Claims 70-226 under 35 U.S.C. 112, first paragraph, because the specification, for lacking a fully-enabling scope, are withdrawn.

The rejections are withdrawn because it was well known in the art to use adenoviruses for gene therapy. Moreover, Applicant's disclosure is generic to adenovirus preparation, not to gene therapy, and hence, their preparations of adenoviruses may be used in other adenoviruses.

Moreover, with regard to specific levels of purity, etc., the rejections are withdrawn as to the method of making because (1) many steps are known in the art for the various steps claimed,

and (2) no art exists to evince doubt that any level of purity may be obtained. Therefore, to use the known in the art for making and purifying adenovirus and obtain the levels of purity required, would simply be such experimentation that is routine in the art.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

In light of Applicant's amendments, the rejections of Claims 70-78, 83, and 85-100 under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over

Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, are withdrawn.

The rejections are withdrawn on the basis that Neither Zhang nor Huyghe teach or suggest the use of serum-free media to grow cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 70-78 and 80-100 remain rejected, under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50, for reasons of record.

It is noted that the claims now require serum free media for the growth of the cells, and hence, all the previous rejections of claims 70-78 and 80-100 now require Perrin, et al., for the teaching of serum free media; hence, the previous rejections on Zhang, which are withdrawn (above) now collapse into Zhang (as evidenced by Huyghe) and Perrin, for reasons of record.

Response to Argument – Zhang/Perrin

Applicant's argument of 6/2/06 has been fully considered but is not found persuasive.

Applicant argues that Perrin is directed to the use of rabies virus, which is structurally distinct from that of adenovirus, and therefore, the Artisan would not expect the adenovirus to

grow in such systems, further citing a declaration by Dr. Zhang, received 6/12/06 as a copy of the same declaration made in another Application (pp. 28-29).

Such is not persuasive. While the Examiner acknowledges that these viruses are distinct, none of the summary of the differences in the biology of the viruses appear to have any relevance to the absence of BSA in the culture, i.e., the cells grow in culture, and none of the viral processes appear to be affected by the absence of BSA. Moreover, Dr. Zhang's mere conclusion (in the declaration supplied as Appendix A), without scientific evidence or logical reasoning otherwise, fails to rebut the fact that Perrin provides an art accepted methodology for removing contaminants, such as BSA, in the preparation of culture based pharmaceutical compositions. Perrin is not relied upon for solving any problem in culturing adenovirus, *per se*, rather it is relied on simply to demonstrate that there were art accepted methods for culturing to remove BSA from viral based pharmaceutical compositions. Moreover, Applicant's argument against using such conditions appear inconsistent with respect to the guidance provided in the instant specification, which is effectively the same as the Examiner's (p. 28, lines 8-17), in producing pharmaceutical compositions. Further, with respect to 293 cells, there would be no need to use such cells in order to compliment the adenoviral vectors encompassed by the claims. It is noted that the different mechanisms of the virus appear to have to little to do with the fact that the cells function in the media of Perrin. Moreover, if they are found to be so functional, there exists no reason to doubt that the adenovirus could be grown.

Applicant argues that no motivation to combine Perrin with the other references exists (p. 28).

Such is not persuasive. The Examiner has cited several reasons why this reference would be combined with the other references (Official Action of 12/16/05, p. 20, paragraph 4).

Applicant argues that the Art supplied does not provide motivation to combine the teachings of Perrin with the teachings of perfusion, roller bottles, etc., as taught by the other references (p. 29).

Such is not persuasive. As was stated, these are known methods of growing the cells and providing nutrients, etc., and hence, these methods, well known in the art, are the ones which the artisan would use (Official Action of 12/16/05, p. 20, paragraph 3). Further, it is noted that the specification teaches that comparison or use of different methodologies appear to be equivalent (p. 28, line 23).

Claim Rejections - 35 USC § 103 – Zhang(Huyghe), Perrin, and Nadeau/Trepanier

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

While, in light of the amendments, the rejection of Claim 74 under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416 and Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11, is withdrawn due to the fact that the references do not teach or suggest serum-free media;

Claim 74 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Claims 70-78 and 80-100 remain rejected, under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50, for reasons of record, as applied to claim 70 above, and as further evidenced by Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11.

The rejection is now maintained on the new basis, due to Applicant's claiming of serum free media in the base claim, requiring the Perrin reference to make the rejection.

As is shown above, Zhang, Huyghe and Perrin teach the various aspects of claim 70; however, they do not specifically discuss nucleic acid contaminations less than 0.2ng/mL.

On the other hand, the other two references (Nadeau and Trepanier) teach the use of ultrafiltration in the purification of viral particles (e.g., Nadeau, p. 615, col. 1, paragraph 1). As such, these steps are generally known in the art. Moreover, Applicant's specification makes clear that such ultrafiltration step yields the desired levels of contaminating nucleic acids (SPECIFICATION, TABLE 10). Hence, such ultrafiltration would necessarily yield the desired levels of contaminating nucleic acid.

At the time of invention by Applicant it would have been obvious to modify the methods of Zhang (Huyghe) and Perrin, by the ultrafiltration step of either Nadeau or Trepanier. One would have been motivated to do so because such steps are known in the art for concentration and purifying adenovirus. Moreover, the Artisan would have had a reasonable expectation of success, as these methods were already known successful.

Response to Argument – Zhang(Huyghe)/Perrin/Nadeau or Trepanier

Applicant's argument of 6/12/06 has been fully considered but is not found persuasive.

Applicant's argument has been fully addressed above, with respect to the rejections including claim 70, above. Hence, such argument is similarly not persuasive for the same reasons.

Claim Rejections - 35 USC § 103 – Zhang/Perrin

Claims 101, 102-105, and 106-131 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416 as applied to claims 70-78, 83, and 85-100 above, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50 for reasons of record.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Response to Argument – Zhang/Perrin

Applicant's argument of 6/12/06 has been fully considered but is not found persuasive.

Applicant's argument has been fully addressed above, with respect to the rejections including claim 70, above. Hence, such argument is similarly not persuasive for the same reasons.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 132, 133-136, and 137-162 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and Perrin, et al. (1995) Vaccine, 13(13): 1244-50, for reasons of record.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Response to Argument – Zhang/Perrin

Applicant's argument of 6/12/06 has been fully considered but is not found persuasive.

Applicant's argument has been fully addressed above, with respect to the rejections including claim 70, above. Hence, such argument is similarly not persuasive for the same reasons.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 105 remains further rejected under 35 U.S.C. 103(a) as being unpatentable over over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50 as applied to claim 101 above, and further in view of Nadeau,

et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11, for reasons of record.

Response to Argument – Zhang, (Huyghe), Perrin and Nadeau/Trepanier

Applicant's argument of 6/12/06 has been fully considered but is not found persuasive.

Applicant's argument has been fully addressed above, with respect to the rejections including claim 70, above. Hence, such argument is similarly not persuasive for the same reasons.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

In light of the amendments, the rejections of Claims 163, 164-167, 168-171, 176, and 178-193 remain rejected, under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and in view of Graham, et al. (1991) Methods in Molecular Biology, vol. 7, Ed. By Murray, published by Humana Press, Inc., Clifton, NJ., pp. 109-128, for reasons of record, are withdrawn.

Specifically, the references cited do not teach a bioreactor or microcarrier.

Claim Rejections - 35 USC § 103

Claims 163-175 and 177-193 remain rejected, and claim 176 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and Graham, et al. (1991) Methods in Molecular Biology, vol. 7, Ed. By Murray, published by Humana Press, Inc., Clifton, NJ., pp. 109-128 as applied to claims 163-171 and 178-193, above, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50, for reasons of record and/or the reasons provided below.

As shown above, Zhang and Graham obviate the limitations of the claims 163-171, and 178-197, as further evidenced by Huyghe; however, they do not teach the aspects of bioreactors and/or microcarriers, they do not teach serum free media, bioreactors, microcarriers, or perfusion methods. Further, Zhang and Graham do not specifically teach BSA levels below the detection limit of western blots or essentially free of BSA, even though, absent to believe otherwise, the compositions meet these claims. Further, Huyghe teaches feeding the batch (e.g., p. 1404, col. 1, paragraph 5). However, Perrin is now used to specifically teach these limitations.

On the other hand, Perrin teaches the use of serum-free media to overcome various problems (p. 1244, col. 2, paragraph 2-p. 1245, col. 1, paragraph 1). Moreover, Applicant teaches that the levels of BSA are caused by use of serum-free media (e.g., SPECIFICATION, p. 92, paragraph 2). With regard to the use of bioreactors and microcarriers, Perrin teaches that it was standard in the art to use such bioreactors with such microcarriers (p. 1244, col. 2, paragraph 2), as well as the use of perfusion techniques and roller-bottles (id.).

At the time of invention by Applicant, it would have been obvious to modify the methods of Zhang and Graham with the steps of Perrin. The Artisan would have been motivated to do so because such methods were standard in the art. Moreover, the Artisan would have had reasonable expectation of success, as the Art had already demonstrated that such methods are successful in producing virus.

Response to Argument – Zhang/Graham/Perrin

Applicant's argument of 6/12/06 has been fully considered but is not found persuasive.

Applicant's argument has been fully addressed above, with respect to the rejections including claim 70, above. Hence, such argument is similarly not persuasive for the same reasons.

Claim Rejections - 35 USC § 103

Claim 167 remains further rejected under 35 U.S.C. 103(a) as being unpatentable Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and in view of Graham, et al. (1991) Methods in Molecular Biology, vol. 7, Ed. By Murray, published by Humana Press, Inc., Clifton, NJ., pp. 109-128, or as further referenced by Perrin, above, and further in view of Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the

absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Response to Argument – Zhang, Nadeau/Trepanier

Applicant's argument of 6/12/06 has been fully considered but is not found persuasive.

Applicant's argument has been fully addressed above, with respect to the rejections including claim 70, above. Hence, such argument is similarly not persuasive for the same reasons.

Claim Rejections - 35 USC § 103

In light of the amendments, the rejections of Claims 194-202, 207, and 209-226 rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, and Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and as further evidenced by Huyghe, for reasons of record, are withdrawn.

The rejections are withdrawn because the art cited in this rejection do not teach or suggest roller bottles or perfusion techniques.

Claim Rejections - 35 USC § 103

Claims 194-226 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, and Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and as further evidenced by Huyghe, as applied to claim 194

previously, above, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50, for reasons of record and/or reasons delineated below.

Response to Argument – Zhang/Huyghe/Perrin

Applicant's argument of 6/12/06 has been fully considered but is not found persuasive.

Applicant's argument has been fully addressed above, with respect to the rejections including claim 70, above. Hence, such argument is similarly not persuasive for the same reasons.

Claim Rejections - 35 USC § 103

Claim 198 remains further rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, and Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and as further referenced by Perrin (ABOVE), and further in view of Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11.

Response to Argument – Zhang/Hughe/Perrin/Nadeau/Trepanier

Applicant's argument of 6/12/06 has been fully considered but is not found persuasive.

Applicant's argument has been fully addressed above, with respect to the rejections including claim 70, above. Hence, such argument is similarly not persuasive for the same reasons.

Conclusion

No Claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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